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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 02/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/021,906	CHEE ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2004 and 17 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 19, 2004 and November 17, 2004 has been entered.

2. Claims 27-43 were previously pending. Applicants did not make any amendments to the claims.

3. Applicants' arguments overcame the rejection of claims 27-43 under 35 U.S.C. 102(e) over Fan et al. All other rejections are maintained for reasons given in the "response to Arguments" section below.

Response to Arguments

4. Applicant's arguments filed August 19, 2004 and November 17, 2004 have been fully considered but they are not persuasive.

A) Regarding the priority date for the instant claims 27-43, since the rejection of the claims as anticipated by Fan et al. is withdrawn, the arguments are no longer relevant.

B) regarding the rejection of claims 27-41 and 43 under 35 U.S.C. 103(a) over Taylor et al. and Walt et al., Applicants argue that because the purpose of the prior art differs from the purpose of Applicants' invention, there is no motivation to combine Taylor et al. with Walt et al.

As to the purpose of Applicants' invention, as stated in the preamble to claim 27, it is detection of amplification reaction, the amplification reaction being RCA, or rolling circle amplification. The purpose of Taylor et al. invention is, as stated in the Abstract: "Disclosed are

methods for detecting nucleic acids using rolling circle-based amplification and arrays of capture probes. Therefore, as far as the purpose is concerned, it seems to be the same in both cases.

Further, as explained in the previous office action, there is ample evidence that Taylor et al. and Walt et al. can be successfully combined by a skilled artisan to arrive at Applicants' invention.

Walt et al. teach a general method of detection of different analytes, including nucleic acids (Table V; col. 10, lines 4-16), on microbead-based arrays, by capturing target sequences with capture probes bound to microspheres. Therefore, Walt et al. teach detection of nucleic acids by capture onto a microbead array with capture probes attached to microbeads, therefore such detection method can be applied to any process in which detection of nucleic acids is desired, such as detection of amplification products.

Taylor specifically teaches, combination of amplification followed by detection of amplification products on microspheres. For example, in paragraph [0003], Taylor teaches

"In general, the invention includes methods which combine isothermal methods of nucleic acid amplification with a positional array analysis. In some embodiments, the array is a three dimensional array, e.g., a gel pad array, analysis. In preferred methods, a target is isothermally amplified, and the amplification product is contacted with a positional array, thereby analyzing a nucleic acid sequence. Examples of isothermal amplification include, rolling circle amplification, nucleic acid sequence-based amplification (NASBA) (see, e.g., U.S. Pat. Nos. 5,409,818 and 5,130,238), self sustained sequence replication (3SR), strand displacement amplification (SDA) (see, e.g., U.S. Pat. Nos. 5,523,204; 5,455,166; 5,631,147; 5,712,124, and 5,733,752), cycling probe reaction or TMA, (see, e.g., U.S. Pat. Nos. 5,554,516; 5,480,784; and 5,399,491)." (emphasis added).

Further, in paragraphs [0052] and [0053], Taylor teaches:

[0052] The selected population of circular sequences is amplified by rolling circle application. The amplified population of sequences from the said rolling circle amplification, e.g., can be amplified further. For example, it can be amplified by rolling circle amplification. The second or subsequent amplifications can be done prior to further analysis. The subsequent rolling circle amplifications can use the same or similar circular sequence as was used in the initial R.C.A. or a different circular sequence. It is also possible that the circular sequence can be, for example, from a closed or open circular template.

[0053] Amplified circles, or cleavage products thereof are applied to an array of a plurality of capture probes, wherein each of the capture probes is positionally distinguishable from other capture probes of the plurality on the array, and wherein each positionally distinguishable capture probe includes a unique (i.e., not repeated in another capture probe) region complementary to the plurality of selector probes;

[0054] hybridizing the amplified sample sequence with the array of capture probes, thereby identifying circular nucleotide sequences that bind to and/or alter the function of proteins or other targets." (emphasis added).

Furthermore, Taylor teaches that cleaved RCA products can be attached to microbeads, and analyzed on a Cantor-type array (U.S. Patent No. 5,503,980). Investigation of the Cantor patent reveals that Cantor-type array is in fact a microbead array, with capture probes attached to microbeads (see, for example, Examples 1 and 13). Therefore, Taylor provides specific connection not only between detection of amplification products on an array, but specifically for the detection of RCA amplification products on a microbead array.

Taylor provides a method of detection of RCA amplification product on arrays, including microbead arrays, whereas Walt et al. teach microbead arrays which are useful in a detection of a

wide range of analytes, including nucleic acids. Both references teach microbeads, and Walt et al. teaches an efficient and inexpensive way of creating an array (col. 3, lines 26-30). Therefore, provided with the teachings of Taylor and Walt et al., a skilled artisan would be motivated to use the microbead array of Walt et al. to detect the microbead amplification products of Taylor.

The rejection is maintained.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 27-41 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor (Publication No. US 2002/0168645 A1) and Walt et al. (U.S. Patent No. 6,023,540).

A) Regarding claims 27, 28, 30, 41 and 43, Taylor teaches detection of nucleic acid using rolling circle amplification. The method comprises hybridizing a single-stranded circular template (= circularized probe) to a sample (= target) nucleic acid, where the circular template has at least one sequence complementary to the target and at least one oligonucleotide which results in a cleavage site in an oligonucleotide multimer (= concatamer), followed by addition of a primer, dNTPs and a polymerase to produce an oligonucleotide multimer, cleavage of the multimer to produce cleaved amplified nucleic acid (= amplicon cleavage products), and contacting the cleavage products with an array of capture probes to detect the amplification products ([0005]-[0011], [0121]).

The circularized probe is prepared by hybridizing each end of a linear oligonucleotide (= circular primer) to a sample sequence, in such a way that a 3' end of the linear oligonucleotide has a

sequence complementary to the 5' end of the target and the 5' end of the linear oligonucleotide has a sequence complementary to the 3' end of the target, and the 5' and 3' ends of the linear oligonucleotide are immediately adjacent to each other, followed by joining the ends of the linear oligonucleotide to form a circularized probe ([0012]-[0014]).

Taylor teaches an extension reaction catalyzed by a polymerase, a linking reaction catalyzed by a ligase and a nucleic acid cleavage reaction catalyzed by a restriction enzyme ([0036]).

Regarding claims 29 and 37-40, Taylor teaches an RCA probe with an interrogation region at its 5' end, which is complementary to an interrogation sequence (= detection position) on the target, and a terminal sequence at its 3' end, complementary to the probe annealing sequence of the target (Fig. 1; [0153-0156], [0164]). The interrogation sequence may contain a polymorphic region, such as a single nucleotide polymorphism (SNP). The interrogation sequence can be positioned at the 3' end of the probe ([0168]). Taylor teaches an RCA probe comprising a restriction endonuclease site ([0159], Fig. 1), a tag sequence (= adapter), which can be used to hybridize the amplified product to a capture probe on the array ([0161], [0162], Fig. 1), and an RCA primer sequence (= amplification priming site), which allows priming of rolling circle amplification ([0163], Fig. 1).

Regarding claim 31, Taylor teaches RCA amplification with labeled nucleotides ([0169]).

Regarding claim 32, Taylor teaches cleavage of the concatamer amplicon with a type II S restriction endonuclease ([0170]).

Regarding claim 33, Taylor teaches arrays on microtiter plates with wells ([0121]).

Regarding claim 35, Taylor teaches substrate of glass or plastic ([0122]).

Regarding claim 43, Taylor teaches target nucleic acid attached to solid support via capture probe (page 2, [0021]-[0023]).

B) Taylor does not teach capture probes attached to microspheres which are randomly distributed on a surface of a substrate, or a substrate being a fiber optic bundle.

C) Regarding claims 27, 34 and 36, Walt et al. teach a microsphere-based analytical system with microspheres carrying different chemical functionalities and positioned in wells of a fiber optic bundle sensor. The population of beads includes separate subpopulations carrying different chemical functionalities (Col. 3, lines 18-31; col. 4, lines 4-15). The microbeads are randomly distributed in an array (col. 4, lines 9-14). Each microsphere subpopulation contains different reporter dye, which may be fluorescent (col. 5, lines 40-52). The functionalites attached to the microspheres can be oligonucleotide probes (capture probes) (col. 10, lines 4-17, Table V).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to perform the nucleic acid detection methods of Taylor on an array of Walt et al. The motivation to do so, provided by Walt et al., would have been that fiber-optic sensor supported a large number of chemical functionalities and was easy to use and manufacture.

7. Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor and Walt et al. as applied to claim 27 above, and further in view of Lizardi (U.S. Patent No. 5,854,033; cited in the IDS).

A) Claim 42 is drawn to the circular primer hybridizing to target nucleic acid in such a way that it's 5' end and 3' end are not immediately adjacent and contacting the hybridization complex with a polymerase which fills the gap between the two ends of the primer.

B) Taylor teaches a probe which has the 5' and 3' ends immediately adjacent to each other upon binding to the target, but does not teach a gap between the ends of the probe.

C) Lizardi teaches an open circle probe which can bind to the target nucleic acid in such a way that it's 5' and 3' ends are separated by a gap, which can then be filled by a polymerase (col. 5, lines 25-28; col. 6, lines 39-46; Fig. 2).

It would have been *prima facie* obvious to one of ordinary skill in the art to have used a probe of Lizardi in the combined method of Taylor and Walt et al. The motivation to do so, provided by Lizardi, would have been that using gaps between the ends of the probe allowed amplification of different allelic variants of the target sequence.

8. No claims are allowed.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS
February 7, 2005

JEFFREY FREDMAN
PRIMARY EXAMINER